Spinal Deformities in Marfan Syndrome

Constantine A. Demetracopoulos, MD, Paul D. Sponseller, MD*

Department of Orthopaedic Surgery, Johns Hopkins Medical Institutions, The Johns Hopkins Hospital, 601 North Caroline Street, Room 5253, Baltimore, MD 21287, USA

Marfan syndrome (MFS) is an autosomal dominant disorder of connective tissue that displays complete penetrance but variable expression [1]. Genetic studies localized the FBN1 gene responsible for MFS disease to chromosome 15q21 [1,2]. More than 135 mutations in the fibrillin gene have been identified, and 70% of affected individuals have an identifiable FBN1 mutation [3]. Patients who have Marfan disorder are believed to have a defect in the synthesis, secretion, or incorporation of fibrillin, a glycoprotein that is a major component of various types of connective tissue, including bone [3]. Thus, MFS is a multisystem disease, and manifestations are seen most commonly in the ocular, cardiovascular, and skeletal systems.

The prevalence of MFS is estimated at two to three cases per 10,000 individuals [4]. Approximately 15% to 25% of patients do not have a family history of MFS and may represent de novo mutations [3,4]. MFS is a pleiotropic condition, and findings tend to become more apparent with age. One end of the spectrum represents patients who are affected only mildly, whereas the other end represents patients who have a severe neonatal form who may encounter cardiovascular complications during the first year of life. The most apparent clinical findings in MFS involve the skeleton (arachnodactyly, scoliosis and thoracic lordosis, dolichostenomelia, sternal deformities, and joint laxity). Although these findings are not specific when found individually, the presence of multiple findings should prompt a referral to genetics or the echocardiography laboratory.

Diagnosis

Although genetic testing is available, it is complex and not highly sensitive. As a result, MFS remains a clinical diagnosis. According to the diagnostic (Ghent) criteria, the diagnosis can be made with the presence of at least one major criterion in two organ systems and the involvement of a third system or one major criterion in an organ system and the involvement of a second system when there is a positive family history of MFS or documentation of a FBN1 mutation (Box 1) [5]. Major criteria are named as such because they are infrequent in other conditions and carry high diagnostic specificity when present. The differential diagnosis includes homocystinuria, congenital contractual arachnodactyly, Stickler syndrome, Ehlers-Danlos syndrome, MASS (mitral, aortic, skin, and skeletal manifestations) phenotype, Loeys-Dietz syndrome, and Schprintzen-Goldberg syndrome [6]. Early diagnosis is of the utmost importance to initiate prophylactic β-blockade therapy, which has been shown to be effective in slowing the rate of aortic dilatation and reducing the development of aortic complications in patients who have MFS [7].

Vertebral morphology

The classic “Marfan spine” features may include increased vertebral scalloping, a higher prevalence of lumbosacral transitional vertebrae, lengthened transverse process distance, and a reduction in pedicle width and laminar thickness [8,9]. Mean pedicle widths from L1–L3 were smaller than the smallest available pedicle screw (5 mm) in a study of 32 patients who had MFS. In addition, laminar thickness from L1–L5 was significantly less in patients who had MFS than...
in normal controls [9]. Many patients also have significant scalloping of the sacrum inside the spinal canal (Fig. 1). Therefore, careful preoperative planning of fixation anchors, possibly including CT, may be necessary.

### Scoliosis and kyphosis

Because the spine depends upon a balance of forces during growth, conditions that disrupt the musculoskeletal matrix will cause spinal deformity. In a large cross-sectional study, the

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**Box 1. The Ghent diagnostic criteria for Marfan syndrome**

**Skeletal system**
- **Major criteria:** presence of at least four of the following:
  - Pectus carinatum
  - Pectus excavatum requiring surgery
  - Reduced upper to lower segment ratio or arm span to height ratio > 1.05
  - Wrist sign (thumb and fifth digit overlap circling the wrist) and thumb sign (distal phalanx protrudes beyond border of clenched fist)
  - Reduced extension at the elbows (°)
  - Scoliosis > 20°
  - Pes planus
  - Protrusio acetabuli of any degree (ascertained on radiographs)
- **Minor criteria**
  - Pectus excavatum
  - Joint hypermobility
  - High arched palate
  - Facial
    - Dolicocephaly
    - Malar hypoplasia
    - Enophthalmos
    - Retrognathia
    - Down-slanting palpebral fissures

**Ocular system**
- **Major criterion**
  - Ectopia lentis
- **Minor criteria**
  - Flat cornea
  - Increased axial length of the globe (> 23.5 mm)

**Cardiovascular system**
- **Major criteria**
  - Dilatation of the ascending aorta
  - Dissection of the ascending aorta
- **Minor criteria**
  - Mitral valve prolapse with or without mitral valve regurgitation
  - Dilatation of the main pulmonary artery in the absence of valvular or peripheral pulmonic stenosis (age < 40)
  - Calcification of the mitral annulus before the age of 40 years

- **Pulmonary system**
- **Minor criteria (only)**
  - Spontaneous pneumothorax
  - Apical blebs

**Skin and integumentary system**
- **Minor criteria (only)**
  - Striae atrophicae
  - Recurrent or incisional hernia

**Neurologic system**
- **Major criterion**
  - Lumbosacral dural ectasia by CT or MRI

**Family/genetic history**
- **Major criteria**
  - First-degree relative who independently meets the diagnostic criteria
  - Presence of mutation in FBN1 gene
  - Presence of haplotype around FBN1 inherited by descent and unequivocally associated with diagnosed MFS in the family

The index case requires major criteria in two different organ systems and involvement of a third. If the FBN-1 mutation is present, then one major criterion and involvement of a second organ system suffices.

A relative of the index case requires one major criterion in family history and one major criterion in an organ system and involvement of a second organ system.
prevalence of scoliosis was 63% in MFS [10]; however, many of the curves were minor, and only 10% to 20% required treatment of any kind. The curve patterns were similar to those seen in idiopathic scoliosis, with the most common types being thoracolumbar and thoracic, although there was a higher rate of triple curves [10]. Differences were seen in the sagittal plane, however (see later discussion). Scoliosis progresses at a faster rate in MFS than in the general population in all age groups, with the greatest progression occurring in patients who are 3 years old or younger (19° ± 17° per year) [10]. Virtually all curves greater than 30° in immature patients reach at least 40° at maturity. Curves greater than 40° increase during adulthood, at a slightly higher rate than idiopathic scoliosis. Curves greater than 50° progress at a mean rate of 3° ± 4° per year in adulthood [10]. Patients who had MFS and scoliosis had more back pain than those who did not have scoliosis.

Brace treatment does not seem to have as much success in MFS as in idiopathic scoliosis. One study reported a 17% success rate for bracing scoliosis curves in MFS. Thus, bracing is recommended mainly for growing children with curves in the range of 15° to 25°. Patients with curves of 25° to 45° may be offered the option of using the brace; however, patients and physicians should be aware that there is only a one in five chance of controlling the curve successfully. Bracing is not recommended for curves greater than 40°, except as a temporizing option; the curve will likely increase [11].

Infantile scoliosis is a special challenge to treat in MFS. Bracing has a limited role, especially in smaller curves. It is mainly useful in promoting upright posture in patients with a coexistent kyphosis. Also, surgery is especially challenging for patients younger than 4 years of age. In addition to typical difficulties encountered when operating on the young child for scoliosis, because of thin body habitus and a paucity of local, durable soft tissues, instrumentation is hard to cover in young patients who have MFS. The use of a growing rod using iliac fixation distally and strong proximal anchorage has been successful in these cases (Fig. 2). Eventual fusion will be necessary.

Sagittal plane deformities also are common in MFS. The mean kyphosis in the population that has MFS is greater than in the general population. Forty percent of patients who have MFS have a kyphosis greater than 50° [10]. Different types of sagittal alignment were found: hypokyphosis, hyperkyphosis, and thoracolumbar kyphosis with compensatory thoracic lordosis [10]. Sponseller and colleagues [10] proposed a classification
system for the sagittal deformity associated with MFS (Fig. 3).

**Dural ectasia**

Dural ectasia (DE), a widening of the dural sac and nerve root sleeves in the caudal portion of the spine, is rare in the normal population but it has a high prevalence (56% to 92%) in the adult population that has MFS (Fig. 4) [12–14]. The dural sac is enlarged mainly below the level of L5 [13–18]. Among 73 patients who were diagnosed with MFS, Rose and colleagues [19] found DE to be the second most common major manifestation. DE worsens with age, and a recent study on a murine model of MFS suggests that DE is the result of hydrostatic pressure exerted upon an inherently weakened dura [20]. In children, symptoms may be mild or not present at all. In a prospective patient-control study of patients between 4 and 18 years of age, Knirsch and colleagues [21] found MRI evidence suggestive of DE in up to 40% of children. The consequences of DE include bony erosion that may lead to anterior meningocele or posterior meningocele. Clinically, patients who have DE may present with headache, proximal leg pain, leg weakness and numbness, abdominal pain, and genital and rectal pain [22]. DE also has been associated with moderate to severe back pain; however, as many as 41% of patients who have DE have no back pain at all [23]. Sometimes DE is completely asymptomatic [23–30].

There are several definitions of DE. Fattori and colleagues [31] used morphologic criteria consisting of bulging of the dural sac, lack of epidural fat at the level of the posterior wall of at least one posterior vertebral body, and the presence of radicular cysts on MRI to grade the degree of dural abnormality. Villeirs and colleagues [32] used CT of the spine to establish a quantitative method of assessing for DE by defining the normal ratio of the transverse diameter of the dural sac to the

Fig. 3. Types of sagittal profiles in patients who have MFS. (A) In type I sagittal alignment, the transition zone between the kyphotic and lordotic segments is at or above L2. Subtype IA corresponds to normal kyphosis and lordosis, subtype IB describes thoracic kyphosis less than 20°, and subtype IC refers to thoracic kyphosis greater than 50°. (B) In type II sagittal alignment, the transition zone is caudad to L2. Subtype IIA refers to a thoracolumbar kyphosis that extends caudad to L2; subtype IIB indicates a reversal of normal contours with thoracic lordosis, thoracolumbar kyphosis, and low lumbar lordosis. (From Sponseller PD, Hobbs W, Riley LH 3rd, et al. The thoracolumbar spine in Marfan syndrome. J Bone Joint Surg Am 1995;77(6):868; with permission.)

Fig. 4. DE in MFS.
transverse diameter of each lumbar vertebral body. Oosterhof and colleagues [33] used MRI to calculate dural sac ratios in the anteroposterior plane; they found that abnormal dural sac ratios at L3 and S1 could be used to identify MFS with 95% sensitivity and 98% specificity. Ahn and colleagues [15] suggested that the “gold standard” for the diagnosis of DE is a dural volume greater than 7 cm³ when measured caudal to the inferior endplate of L5; however, because techniques to calculate dural volume from reconstructed sacral spine MRIs are not widely available, Ahn and colleagues [15] used MRI and CT to identify two major criteria and two minor criteria indicative of DE in patients who have MFS. Major criteria included a sagittal diameter of the spinal canal at S1 or below greater than the sagittal midaxis of L4 or above and the presence of an anterior meningocele. Minor criteria included scalloping at S1 and an enlarged L5 nerve root sleeve diameter. When at least one major or two minor criteria were present, DE was diagnosed with a sensitivity of 87% and a specificity of 95% using MRI, and a sensitivity of 83% and a specificity of 90% using CT. In a separate study, Ahn and colleagues [34] examined the effectiveness of conventional radiography to detect DE in patients who had MFS. They determined that the presence of an interpediculate distance at L4 of at least 38.0 mm, a sagittal canal diameter at S1 of at least 18.0 mm, or a scalloping value at L5 of at least 5.5 mm can detect DE with a specificity of 91.7% and a sensitivity of 57.1%.

Weigang and colleagues [35] and others have evaluated the efficacy of the MRI and CT criteria proposed for the diagnosis of DE (Table 1). Weigang and colleagues [35] found only two patients who had MFS who satisfied all criteria for DE using the three methods proposed by Villeirs and colleagues, Oosterhof and colleagues, and Ahn and colleagues in a group of 18 individuals who had MFS and 23 individuals who did not have MFS. Moreover, DE was found in up to 44% of normal controls. Because a “gold standard” was not used, the sensitivity and specificity of each method cannot be calculated from this study; however, it suggests that the various methods available to assess for DE can produce varying

Table 1
Comparison of four methods for detecting dural ectasia on MRI in individuals who do and do not have Marfan syndrome

<table>
<thead>
<tr>
<th>Method</th>
<th>Criterion</th>
<th>MFS</th>
<th>Non-MFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oosterhof et al [33]</td>
<td>Increased dural sac ratio at L3 and S1</td>
<td>94%</td>
<td>44%</td>
</tr>
<tr>
<td>Villeirs et al [32]</td>
<td>Increased spinal canal index or dural sac index</td>
<td>18%</td>
<td>0%</td>
</tr>
<tr>
<td>Fattori et al [31]</td>
<td>Presence of a rectilinear dural sac, bulging of the dural sac, lack of epidural fat at the posterior wall of vertebral bodies, radicular cysts, or anterior sacral meningocele</td>
<td>92%</td>
<td>0%</td>
</tr>
<tr>
<td>Ahn et al [15]</td>
<td>Sagittal diameter of the spinal canal at or below S1 is greater than the sagittal diameter at the midaxis of L4 or above</td>
<td>72%</td>
<td>44%</td>
</tr>
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</table>

a Dural sac ratio is the ratio of the anteroposterior (AP) diameter of the dural sac to the AP diameter of the vertebral body.

b Spinal canal index is the sum of the transverse diameters of the spinal canal measured from L1–S1 divided by the sum of the transverse diameters of the vertebral bodies from L1–L4.

c Dural sac index is the sum of the transverse diameters of the dural sac measured from L1–S1 divided by the sum of the transverse diameters of the vertebral bodies from L1–L4.

results, which makes the diagnosis of DE challenging. In a similar study, Habermann and colleagues [36] evaluated the available MRI criteria for the diagnosis of DE in children and adolescents. They determined that abnormal ratios of the midsagittal diameter of the vertebral bodies to the sagittal dural sac diameters at L5 and S1 and a sagittal dural sac width at S1 greater than at L4 were the only statistically significant criteria for DE when children and adolescents who had MFS were compared with normal controls.

**Surgical correction of kyphoscoliosis**

Spine surgery is required in about 10% to 15% of patients (Fig. 5) [10,37]. A medical specialist should be involved to comanage cardiac medications and other issues and to assist with anticoagulation management if there is an artificial heart valve. An MRI or CT should be done of the area of interest before any spine surgery to visualize the bony and dural structures. Intraoperative complications include increased bleeding and cerebrospinal fluid leak. A recent retrospective review of patients who had MFS who underwent surgical correction for spinal deformity found that patients who underwent posterior fusion for scoliosis had an average blood loss of 2150 mL, whereas patients who required revision had an average blood loss of 5300 mL [38]. We have found aprotinin to be helpful in decreasing blood loss. Cerebrospinal fluid leak occurs because of the DE, and dural tears occurred in 8% of patients.

Fig. 5. Severe kyphoscoliosis in a 16-year-old who has MFS. (A) Preoperative clinical appearance. (B) Lateral radiograph shows a 95° scoliosis. (C) CT shows bridging of vertebrae. (D) Clinical coronal appearance. (E) Coronal film showing a 95° kyphosis. The patient underwent apical wedge resections and fusions from a posterior approach. (F) Postoperative sagittal appearance. Postoperative lateral (G) and coronal (H) radiographs.
undergoing posterior fusion [38,39]. It can be minimized by keeping the patient in a slight Trendelenburg position intraoperatively and minimizing dissection inside the canal. If a leak occurs, closure is possible sometimes; if not, a dural patch and postoperative bed rest for 2 to 3 days have been successful. Postoperative complications include failure of fixation, adding on of curvature, and pseudarthrosis [37,40]. In a review of 39 patients who had MFS and underwent surgical correction, Jones and colleagues [38] reported a fixation failure rate of 21% and a pseudarthrosis rate of 10%. When correcting spinal deformity, it is important not to fuse too short a segment of spine (Fig. 6). If patients have dysplastic vertebrae, fusions that need to extend to L4 may be better off carried to the sacrum to prevent late pain and decompensation (Fig. 7). The surgeon probably should not use selective thoracic fusion for double major curves unless the lumbar curve is minor. Lipton and colleagues [41] analyzed data of patients who had MFS and underwent posterior spinal arthrodesis. They compared postoperative curve progression between patients who had primary and secondary curves fused completely and patients who had complete fusion of the primary curve and partial fusion of the secondary curve. Preoperative curve characteristics were not compared between groups; therefore, it is unclear whether any differences existed between the two groups preoperatively. Postoperatively, none of the 7 patients who had both curves fused progressed more than 10° at last follow-up; however, 11 of the 16 patients who had partial fusion of the secondary curve progressed more than 10° at last follow-up. It also is important to take into account any unusual kyphosis that may be

Fig. 6. Adding-on deformity after correction of scoliosis in a 12-year old.

Fig. 7. Fusion in a patient who has MFS with dysplastic vertebrae that was carried to the sacrum to prevent late pain and decompensation. (A) Preoperative anteroposterior (AP) radiograph. (B) Postoperative AP coned view.
Failure of fixation is common and is due to ligamentous laxity that allows hooks to dislodge from laminae. In a review of 23 patients who had MFS and underwent surgery for spinal deformity, Di Silvestre and colleagues [39] found a distal hook dislodgement rate of 22%. Problems also may occur with pedicle screw fixation, with screws at risk for losing fixation because of thin pedicles. The surgeon should critically assess the fixation and work to achieve a stable proximal and distal foundation in every patient.

### Spondylolisthesis

The prevalence of spondylolisthesis in the general population is approximately 3%, and, of this population, the mean slip is approximately 15% [42]. In one study, 6% of the population that had MFS had spondylolisthesis of the fifth lumbar vertebra or the first sacral vertebra with a mean slip of 30% [10]. It is at this level where DE, sacral scalloping, and potential cerebrospinal fluid leaks have the greatest clinical importance. Although the frequency of spondylolisthesis in patients who have MFS may not be markedly higher than in the general population, if a slip is present, the altered tissue properties allow greater forward slip to occur. In patients who have MFS and scoliosis of at least 10°, mean slip was 60% [10].

### Cervical spine

Hobbs and colleagues [43] conducted a radiographic analysis of the cervical spine in patients who had MFS, which revealed an increased prevalence of focal kyphosis and a slightly increased atlantoaxial movement with flexion and extension. Herzka and colleagues [44] reported three cases that suggested that children who have MFS might be at risk for atlantoaxial rotatory subluxation when muscle tone is attenuated by general anesthesia or muscle relaxants. Special attention to intubation and positioning, intraoperatively and postoperatively, may be warranted, and rotatory subluxation should be included in the differential diagnosis for patients who have MFS and neck pain.

### Bone density

Abnormal fibrillin in the population that has MFS may play a role in bone mineralization. Carter and colleagues [45] demonstrated that there is a reduced axial bone mineral density (BMD) in men and women who have MFS; they postulated that this may be due to mutations of the fibrillin gene or environmental issues, such as reduced exercise that leads to suboptimal peak bone mass. Giampietro and colleagues [46] reviewed 51 patients who had MFS and found that the average BMD in the femoral necks of adult male patients was significantly less than in normal controls; however, average BMD measurements for female and adolescent patients who had MFS were within normal limits. Therefore, more research may be necessary before implementing widespread BMD evaluations by Dual Energy X-Ray Absorptiometry scans.

### Screening and athletics

It is recommended that patients who have MFS avoid physical stress, because many aortic dissections occur during these events [47–49]. Pyeritz and Dietz [47] recommended that the physician counsel patients on an individual basis. For example, a child with only a slightly dilated aortic root does not need outright restriction but should be counseled away from competitive athletics. Conversely, an older patient with a dilated aortic root should be advised against any sort of strenuous exertion, especially activities with sudden stops (eg, basketball). Furthermore, reports of increased atlantoaxial translation in MFS suggest they should avoid contact sports, which place high-impact loads on the cervical spine. Other activities, such as low-intensity isokinetic sports, should be encouraged.

### Summary

MFS is a disease of connective tissue that affects multiple organ systems. Skeletal manifestations are common at an early age and offer clinicians the opportunity to make a timely diagnosis. Thus, the surgeon examining the spine must be aware of the manifestations of MFS and be able to recognize affected individuals. Spinal deformities are frequent, progress with age, and are less responsive to conservative treatment. Surgical management presents unique intraoperative and postoperative challenges because complication and revision rates are greater in patients who have MFS; however, with attention to detail, excellent results are possible.
References


